MYLAN PHARMACEUTICALS INC

781 Chestnut Ridge Road • P. O. Box 4310 • Morgantown, West Virginia 26504-4310 U.S.A. • (304) 599-2595

October 25, 1999

Food and Drug Administration
Dockets Management Branch (HFA-305)
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: DRAFT GUIDANCE FOR INDUSTRY ON ANDA's: BLEND UNIFORMITY ANALYSIS [DOCKET NO. 99D-2635]

Dear Sir or Madam:

Mylan Pharmaceuticals Inc. (Mylan) would like to take this opportunity to comment on the FDA's Draft Guidance for Industry on ANDA's: Blend Uniformity Analysis.

Mylan believes that the need for blend uniformity analysis (BUA) as a routine in-process control is an issue of great concern within the pharmaceutical industry and that this issue should be handled in a comprehensive and scientifically valid manner which adequately addresses the concerns of all involved parties. At the present time Mylan does not believe that issuance of the subject guidance would be in the best interest of consumers, the FDA or the pharmaceutical industry. Based on the concerns currently being expressed by the pharmaceutical industry regarding this guidance and the unresolved issues previously raised with regard to conducting blend uniformity analysis, Mylan strongly recommends that this draft guidance be held in abeyance until such time that sufficient information and data is generated to scientifically support the issuance of a guidance on this subject.

Mylan's recommendation concerning this guidance is based on the following:

1) Although adequacy of mixing to assure uniformity and homogeneity is one of the control procedures listed in 21 CFR 211.110(a) it is not mandated that BUA be conducted to satisfy this criterion nor is it suggested that BUA be routinely conducted on all production batches. In 21 CFR 211.110(a) it states that five "control procedures" shall be used "where appropriate." The phrase "where appropriate" has been deleted from the Agency's guidance document and significant concern has been expressed by the pharmaceutical industry that BUA is not an appropriate in-process test. In addition, it has long been practiced that by validating the aspect of blend uniformity, or any other in-process attribute, a company can and should eliminate the need to do repetitive, in-process batch testing, as long as adequate controls are in place to assure that the process has not changed from its validated state.

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2) It is Mylan's continued belief that BUA should not be required after a manufacturing process has been validated. Following process validation, BUA for each production batch is considered redundant when finished product content uniformity analysis and assay analysis are routinely performed. If required for every batch, BUA becomes a process validation exercise for every lot of drug product produced. This would certainly result in increased product costs due to added testing and investigative resources, would be time consuming and would provide no added benefit to the safety, efficacy or quality of drug products.

3) The proposed BUA guidance states that FDA intends to seek the support of the Product Quality Research Institute on BUA and that the guidance will be updated based on the outcome of any research. Mylan recommends that this research be conducted prior to the issuance of a final guidance on BUA and that the results of such research be used to scientifically support the guidance, should a guidance be considered necessary based on the research findings.

4) It is well known that current techniques for obtaining samples for BUA result in a high level of variability. Although this issue itself is of utmost concern, it is further compounded by the fact that the proposed guidance does not allow for a two-tiered acceptance criteria. A two-tiered acceptance criteria is considered necessary to allow for variability due to sampling errors influenced by the design of the sampling instrument, sampling technique, and the characteristics of the blend. The lack of a two-tiered approach is considered overly restrictive and is inconsistent with the compendial acceptance criteria for finished product content uniformity testing.

In summary, Mylan recommends that the Agency's draft BUA guidance not be finalized or implemented at this time. We further recommend that this draft guidance be held in abeyance until the Product Quality Research Institute has conducted its research and provided their results and recommendations to the Agency. The concerns surrounding this issue warrant that a comprehensive and collaborative scientific approach be taken in order to address and satisfy the interests of all involved parties.

Sincerely,

Frank R. Sisto
Vice President
Regulatory Affairs

FRS/tlr

FRANK SISTO
MYLAN PHARMACEUTICALS, INC
3711 COLLINS FERRY RD.
MORGANTOWN WV 26505
(304)599-2595

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